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# Chlorinated Paraffin Levels in Relation to Other Persistent Organic Pollutants Found in Pooled Human Milk Samples from Primiparous Mothers in 53 Countries

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**Background:** The current production and use of chlorinated paraffins (CPs) at >1 million tons/y likely exceeds the lifetime production of polychlorinated biphenyls (PCBs). These persistent organic pollutants (POPs) are a concern to human health.

**Objectives:** The United Nations Environment Programme conducts global surveys of human milk samples from individual countries as a noninvasive method of investigating levels and trends in human exposures to POPs such as CPs. We measured CP concentrations and assessed their relation to other POPs in pooled samples collected during 2012–2019.

**Methods:** We analyzed 57 official nationwide pooled milk samples from 53 countries on five continents (Africa, Central/South America, Asia, Europe, and Australia/Oceania). CP concentrations were further characterized by subgroups and compared with concentrations of 19 other POPs, including PCBs and a variety of pesticides.

**Results:** CPs were detected in pooled samples from all 53 countries, with concentrations of 23–700 ng/g lipid. CPs accounted for 18–46% of the total summed POPs in human milk, second only to dichlorodiphenyltrichloroethane (DDT). CP concentrations exceeded PCB concentrations in pooled samples from most countries.

**Discussion:** The presence of CPs in all samples, including samples from isolated locations (e.g., Pacific Island countries), emphasizes the ubiquitous presence of these compounds, whereas differences in subgroup ratios indicate a delay in the shift toward nonregulated medium-chain CPs (MCCPs) for these regions. The predominance of MCCPs in samples from many countries suggests a need for regulation and research on health effects. https://doi.org/10.1289/EHP7696

## Introduction

Chlorinated paraffins (CPs) are mixtures of several thousand compounds that are produced by the chlorination of alkane feedstock (Fiedler 2010). Based on the length of the alkane chains, the resulting technical products are commonly subdivided into short-chain (SCCPs, $C_{10}$–$C_{13}$), medium-chain (MCCPs, $C_{14}$–$C_{17}$) and long-chain CPs (LCCPs, $C_{>17}$) (PARCOM 1995; POPRC 2015). Alkyl chain length composition and the degree of chlorination can be varied to make the resulting products suitable for various industrial applications, some of which have a very high demand (U.S. EPA 2009; Glüge et al. 2016; van Mourik et al. 2016). Such bulk applications include their use as high-temperature lubricants, plasticizers, and flame retardants in a wide variety of products, such as polyvinyl chloride flooring, paints, and leather sealants (ECB 2005, 2008; Gallistl et al. 2018; Hahladakis et al. 2018). Accordingly, the current production volume of CPs is extraordinarily high. The available data indicated a high but widely unperceived production volume until the 1970s (<100,000 tons/y) (Muir et al. 2001), followed by a noticeable annual increase by one order of magnitude that coincided with increasing concerns about the safety of polychlorinated biphenyls (PCBs) as flame retardants and plasticizers and finally their ban (OECD 1973; Breivik et al. 2007). The estimated annual CP production volume of 1.1 million tons in 2015 (Glüge et al. 2016) almost equaled the estimated total production volume of PCBs over six decades (i.e., 1.0–1.5 million tons during 1930–1993) (Breivik et al. 2007; Stockholm Convention 2019).

SCCPs have been under scrutiny for more than a decade for their persistent (Muir et al. 2001; ECHA 2008), bioaccumulative (Fisk et al. 2000; Houde et al. 2008; Yuan et al. 2019), and toxic (Cooley et al. 2001; El-Sayed and Legler 2010; Geng et al. 2016) properties, and their production and use worldwide was severely restricted under the Stockholm Convention in 2017 (COP.8 2017). This action appears to have resulted in a shift to production of the other CP groups, particularly MCCPs and probably LCCPs as well, although data on the latter are much sparser in literature. In anticipation of a likely restriction (POPRC 2006; POPRC and European Union Member States 2006), the production volume of SCCPs only increased gradually after 2005 until the ban in 2017, from 75,000 to ~200,000 tons/y. Simultaneously, the percentage of SCCPs in worldwide CP production dropped from >30% in the 1970s to ~15% in the early 2000s (Muir et al. 2001; Glüge et al. 2016) and remained at this level until 2015. Given the different legal status, it is important to distinguish between SCCPs [listed as persistent organic pollutants (POPs)] and MCCPs [(listed as unregulated, candidate substances of very high concern in the European Union (ECHA 2021)]. LCCPs could not be assigned a benchmark dose level for harmful effects to humans in the European Union (EFSA CONTAM Panel et al. 2020) and were characterized as low risk in the United States (U.S. EPA 2015). Recently, toxicologists have called for more occurrence data and toxicological studies of MCCPs to expand on existing data (Fisk et al. 2000; ECB 2005; Thompson and Vaughan 2014; Yuan et al. 2019) and better assess potential health risks and safety (Swedish Chemicals Agency 2018; EFSA CONTAM Panel et al. 2020; Zellmer et al. 2020). Moreover, MCCPs have been classified as "may cause harm to breastfed children" under the harmonized classification of the EU Classification, Labeling and Packaging (CLP) Regulation (ECHA 2019).

Human milk presents a noninvasive way to monitor POPs levels in the population and is preferable to blood serum for the detection of lipophilic compounds owing to its higher lipid content. Recent studies have reported on the occurrence of PCBs

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(Mamontova et al. 2017; Müller et al. 2017; Bawa et al. 2018) and polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) (Abballe et al. 2008; Fång et al. 2015), several brominated flame retardants (BFRs) (Antignac et al. 2016), organochlorine pesticides (OCPs) (Al Antary et al. 2017; Polanco Rodríguez et al. 2017; Bawa et al. 2018; Chen et al. 2018), and CPs (Cao et al. 2017; Xia et al. 2017a, 2017b; Yang et al. 2018) in human milk. However, the small sample sizes of many studies and high variability due to individual differences between participating mothers hinder comparisons and the evaluation of results from different countries. In addition, some previous studies have been conducted at known contamination hotspots. To overcome these disadvantages, the World Health Organization (WHO) and, later, the United Nations Environment Programme (UNEP) have organized representative global human milk studies since 1987. In addition to analytical advantages, pooled samples provide a very cost-effective way to determine average levels of POPs contamination in individual countries. Initially, the main focus of the studies was PCDD/Fs and PCBs, but new POPs have been added to the portfolio since the inception of the Stockholm Convention in 2004 (Stockholm Convention 2013). For the present study, we report SCCP and MCCP concentrations in pooled human milk samples collected during 2012–2019 from five continents, as well as concentrations of 19 other compounds listed as POPs under the Stockholm Convention. In addition, we report our evaluation of the ratio of SCCPs and MCCPs and their correlation with the other POPs to assess exposure in developing and industrialized countries. Because of their higher molecular weight and consequently lower volatility, LCCPs could not be analyzed by the gas chromatographic (GC) method used in the present study and are therefore not included in this report.

## Material and Methods

### *Study Design*

The UNEP-coordinated exposure studies of POPs in human milk use carefully selected reference laboratories to analyze representative pooled samples from each participating country in order to provide cost-effective and reliable data on POPs background levels in humans. National coordinators for each country obtained permission from their country's ethics board to participate in the study and organized representative sampling campaigns of mothers living outside of known POPs hotspots to facilitate the assessment of background POPs exposures in the general population. Because the primary focus of the study was on PCBs and PCDD/Fs, potential donors living close to waste incinerators and paper factories were excluded from the study. The exact distance defining "close" was decided by the national coordinators and spanned 500 m–5 km (see Supplemental Material, "Sample screening questionnaire 1" and "Sample screening questionnaire 2"). The standardized screening questionnaires for expecting and new mothers were also used to collect data on health history, area of residence, age, dietary habits, occupation, and age, as well as sex of their child; these parameters were used for the selection of eligible donors to contribute to the representative composite (pooled) sample. Eligibility criteria for potential donors included the following:

- Willingness to breastfeed the baby (because the WHO strives to promote breastfeeding)
- Age of the mother (<30 y, to minimize the influence of this predictor)
- Primiparity (in order to have the sample represent the mothers' exposure since birth)
- Only a singleton being expected (not twins or more, to exclude this as a potentially influencing factor)
- A normal, healthy pregnancy (assessed in the screening questionnaire, to avoid putting unnecessary strain on the mother or endangering biosafety of the samples through infectious diseases, such as human immunodeficiency virus or hepatitis C)
- At least 10-y residency in the same area (representing one particular area, thus minimizing potential influences of contamination sources at the previous place(s) of residence)
- No residency near waste incinerators, pulp and paper industries, or, in some countries, metal industries or where chemicals are produced (all of which were identified as potential POP hotspots that would influence results of the pooled samples).

For potential donors identified before the birth of the child, eligibility criteria related to the pregnancy or to the infant (i.e., healthy pregnancy, singleton child) were assessed before sampling to ensure eligibility.

National coordinators were allowed to expand the list of criteria by, for example, adding a minimum age of the mothers or additionally excluding certain areas of residency known to be POPs hotspots according to the National Implementation Plan or the local Official Contact Point as specified by the Stockholm Convention, but the core list of seven eligibility criteria was applied in all countries. Between 2015 and 2020, this questionnaire underwent only minor editorial changes, even though the sampling guidelines as a whole were updated in 2017 (UNEP 2017). Some of the data collected in the screening questionnaires were reported in a summarized way along with the pooled sample (see Supplemental Material, "Sample summary report" and Tables S1 and S2).

Where possible, milk samples were collected 3–8 wk after birth in prenatal clinics under controlled circumstances, but sample collection at home by the mothers or by trained personnel using provided sterilized glassware was also acceptable. Samples collected <3 wk or >8 wk after birth were ineligible for the national pooled samples. An informed consent form was signed by the participants prior to sampling. The correct infant age at the time of sampling and informed consent were mandatory in all participating countries for both surveys presented here.

Of the 50-mL milk sample provided by each participant, 25 mL was used for local analysis of basic POPs (marker PCBs, pesticide POPs, other analytes selected by the national coordinators). The rest was pooled for shipment to the UNEP Reference Laboratories in Freiburg, Germany, where chemicals included in the present report were analyzed, and Örebro, Sweden, where additional chemicals that are not included in this report (specifically, perfluorooctane sulfonate, perfluorooctanoic acid, and other per- and polyfluoroalkyl substances) were analyzed. The pooled samples were preserved by freezing (recommended temperature, −20°C) and, if necessary, by the addition of 0.1% potassium dichromate. The second option was recommended in case frozen storage of the individual samples could not be guaranteed before pooling and for the pooled samples if countries had a hot climate and problems with temperature control. Pooled samples were frozen and shipped with ice packs, and samples were accepted if they were <12°C when they arrived at the laboratory. Dry ice was not recommended because delivery of such hazardous material packages would have required additional logistical efforts. Packages with damaged sample containers were rejected and a new pooled sample requested. In the few cases where markedly less than the required 2.5-L pooled sample was sent, additional sample material was requested and only the initial 12 POPs listed under the Stockholm Convention (Stockholm Convention 2008) analyzed in the meantime. The full description and guidelines for sampling are available online (UNEP 2017). The present study combines data from pooled milk samples collected from countries on five continents during two campaigns, including samples from 12 countries that were collected during 2012–2015, and samples from 41 countries collected during 2016–2019. Fifty countries

submitted one pooled sample representing the whole population, and 3 countries submitted two or more samples collected during the same time period from different population groups or geographical areas within each country. The number and choice of participating countries differed according to the UNEP monitoring scheme, with countries belonging to the Western European and Others Group of the United Nations members (WEOG; including Australia) targeted in 2012–2015, followed by countries in Africa, Central and South America, and members of the United Nations group Pacific Island Countries, in 2016–2019. During both sampling campaigns, countries that were not located in one of the target regions were also allowed to participate at their own cost, including 7 European countries that elected to participate in the program after the first campaign was completed. In addition, countries with high levels of PCBs or PCDD/Fs in pooled samples from previous campaigns (five campaigns spanning 1987 to 2011) were invited to participate again so that data might be used to assess long-term time trends. In accordance with UNEP guidelines and national decisions, we do not report individual country names but, rather, present results for countries grouped by geographical area, namely: South America (SAM), Europe (EUR), Africa (AFR), Central America and the Caribbean (CAM), Asia (ASI), and Australia/Oceania (OCE). However, a list of all participating countries and the years of sampling for each country is provided in Table S3. Duplicate or triplicate pooled samples provided by some countries were each processed and treated as independent samples from the same geographical area in data analyses. Although the time frame of each sampling campaign was dictated by the WHO, specific sampling years varied among countries. Because of a lack of participation in the UNEP surveys, samples and data were not available from the United States or mainland China.

### *Choice of Analytes*

Of all CPs, the subgroups SCCPs and MCCPs ($C_nH_{2n-(2+m)}Cl_m$, $n = 10–17$, $m = 5–n$) were chosen for quantification, because they can be fully analyzed using GC methods and single-chain standards were available. Characterization and concentrations of the standards have been previously described in detail elsewhere (Krätschmer et al. 2019). LCCPs up to a carbon chain length of $C_{20}$ were included in qualitative analyses only because no suitable single-chain standards were available and longer-chained CPs do not transfer completely into the gaseous phase. In addition to SCCPs and MCCPs, we report quantitative data from the same samples for 21 POPs listed in the Stockholm Convention, which were categorized into the following groups:

- Chloropesticides (ΣOCPs): aldrin, chlordane, dichlorodiphenyltrichloroethane (DDT), dieldrin, endrin, heptachlor, mirex, toxaphene, α-/β-/γ-hexachlorocyclohexane (HCH), pentachlorobenzene, pentachlorophenol, chlordecone, and endosulfan
- Polyhalogenated industrial chemicals (ΣIndChem): ΣPCBs [sum of all PCBs calculated as sum of marker PCBs (PCB 28, 52, 101, 138, 153, and 180) multiplied with empirical factor 1.6 according to Schulte and Malisch 1984], hexachlorobenzene (HCB), hexabromobiphenyl (HBB), hexabromocyclododecane (HBCDD), polybrominated diphenyl ethers (PBDEs), and unintentional by-products (e.g., PCDD/Fs).

The summed concentrations of SCCPs, MCCPs, and POPs in both of the groups above are reported as ΣPOPs.

### *Sample Preparation*

For extraction, 50 g of the homogenized pooled sample was centrifuged (3,000 rpm, 4°C) for 10 min to separate the cream. After removing the cream from the hydrous phase, it was dried with anhydrous sodium sulfate, followed by cold extraction with dichloromethane/*n*-hexane (1:1, vol/vol). From this stage on, the method was identical to sample preparation for food as described elsewhere (Krätschmer et al. 2019). In brief, the extract was cleaned of lipids by means of a silica column primed with 45% sulfuric acid. Afterward, coeluting POPs were removed using a Florisil column primed with 1.5% water, eluted with 75 mL *n*-hexane followed by 60 mL of dichloromethane. The second fraction was concentrated by rotary evaporator and under a gentle nitrogen stream before analysis.

### *Instrumental Method and Quantification Strategy*

Both instrumental setup and quantification methods have been described elsewhere (Krätschmer et al. 2018, 2019). In brief, a TRACE 1310 GC system equipped with a 15-m HP-5MS UI capillary column (Agilent Technologies) coupled to a Q Exactive mass spectrometer fitted with an electron capture negative ion (ECNI) source (Thermo Fisher Scientific) was used in a full scan mode (*m/z* 250–810) at 120,000 mass resolution (full width at half maximum, measured at *m/z* 200).

The processing method based on relative response factors calculated according to a Gaussian distribution model included the three most abundant isotope peaks of the $[M–Cl]^-$ or $[M–HCl]^-$ fragment ions of each homolog, extracted by their accurate masses. Briefly, for each SCCP and MCCP chain length, at least three standards with different overall chlorination degrees were injected in order to assess their responses relative to the injection standard ε-HCH. Based on these data, a Gaussian curve was fitted to minimize the sum of squared differences between the different chlorination degrees of each chain length when regarding each homolog separately. Using these homolog-specific, but mostly chlorination-degree independent, response factors, a custom-made mixed SCCP and MCCP standard was characterized before use as a calibration solution. Although the initial design of this mixed standard was based on fish samples (Krätschmer et al. 2019), human milk samples could still be quantified with it because of the nature of the quantification method and the similarities of the CP homolog patterns. LCCPs were only detected as $C_{18}–C_{20}$ CP homologs because longer chain lengths do not transfer into the gaseous phase of the GC. The processing method did not allow for quantification of LCCPs owing to the lack of suitable quantification standards, so we indicate only whether they were present or absent in a given pooled sample (Table 1).

### *Quality Assurance/Quality Control Measures*

CP fragment ions were considered positively identified when retention time, accurate mass, and ion ratios of at least two isotopes matched the applied compound database with theoretical and experimental data on all CP homologs detectable with this instrument setup. Fluctuations due to injection or different tuning were corrected by using ε-HCH (Dr. Ehrenstorfer GmbH, Augsburg, Germany) as the injection standard. Recoveries were calculated using $^{13}C_{10}$-1,5,5,6,6,10-hexachlorodecane (Cambridge Isotope Laboratories, Inc., Tewksbury, MA, USA) as the internal standard. Measurements were carried out using a freshly cleaned and tuned ion source and a new mass calibration to ensure the system was working at optimal conditions. Each sample batch additionally carried quality control samples (spiked and native raw cow's milk) and a procedural blank (sodium sulfate, meant to indicate contamination during sample preparation). Recovery of the quality control samples ranged from 84% to 110%, and blank levels were $0.049 \pm 0.008$ ng/μL (equaling $4.9 \pm 0.8$ ng/extracted sample) ΣSCCPs and $0.023 \pm 0.019$ ng/μL ($2.3 \pm 1.9$ ng/extracted sample) ΣMCCPs over 10 sample sequences. Using the average blank

**Table 1.** Anonymized country-specific results for chlorinated paraffins (CPs), polychlorinated biphenyls (PCBs), the sum of DDT and its metabolites, and the sum of all analyzed persistent organic pollutants [POPs; sum of POPs (ΣPOPs)] in human milk samples ($n = 57$ collected during 2012–2019).

| | | | Concentrations (ng/g lipid) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Area | Sample ID no. | Lipid content (%) | ΣSCCPs | ΣMCCPs | ΣCPs | ΣPCBs[b] | ΣDDT | ΣPOPs | LCCPs detected[a] | ΣSCCP/ΣMCCP | ΣCPs/ΣPCBs |
| AFR | 001 | 3.9 | 52 | 71 | 120 | 81 | 490 | 730 | No | 0.7 | 1.5 |
| AFR | 002 | 4.5 | 40 | 71 | 110 | 36 | 630 | 790 | No | 0.6 | 3.1 |
| AFR | 003 | 4.0 | 50 | 130 | 180 | 22 | 200 | 400 | Yes | 0.4 | 8.0 |
| AFR | 004 | 4.5 | 46 | 94 | 140 | 4 | 110 | 260 | Yes | 0.5 | 36 |
| AFR | 005 | 3.9 | 110 | 170 | 280 | 9 | 560 | 860 | Yes | 0.6 | 30 |
| AFR | 006 | 4.8 | 100 | 210 | 310 | 140 | 190 | 670 | Yes | 0.5 | 2.1 |
| AFR | 007 | 4.9 | 310 | 370 | 680 | 34 | 300 | 1,000 | Yes | 0.9 | 20 |
| AFR | 035 | 4.1 | 70 | 99 | 170 | 1.0 | 7,100 | 7,300 | Yes | 0.7 | 117 |
| AFR | 036 | 4.9 | 69 | 76 | 150 | 23 | 540 | 720 | Yes | 0.9 | 6.4 |
| AFR | 037 | 2.7 | 66 | 93 | 160 | 97 | 240 | 510 | No | 0.7 | 1.6 |
| AFR | 038 | 4.2 | 51 | 47 | 98 | 23 | 99 | 230 | No | 1.1 | 4.2 |
| AFR | 039 | 3.9 | 110 | 200 | 320 | 8 | 550 | 880 | Yes | 0.5 | 39 |
| AFR | 040 | 5.5 | 120 | 100 | 220 | 5.0 | 380 | 610 | No | 1.2 | 41 |
| AFR | 041 | 5.1 | 77 | 80 | 160 | 22 | 77 | 260 | Yes | 1.0 | 7.2 |
| AFR | 042 | 4.0 | 56 | 57 | 110 | 4.0 | 84 | 210 | No | 1.0 | 29 |
| AFR | 043 | 3.5 | 51 | 68 | 120 | 85 | 96 | 310 | No | 0.8 | 1.4 |
| ASI | 008 | 4.6 | 160 | 540 | 700 | 25 | 45 | 850 | No | 0.3 | 28 |
| ASI | 009 | 4.3 | 27 | 38 | 65 | 5.0 | 470 | 550 | No | 0.7 | 13 |
| ASI | 044 | 3.6 | 89 | 88 | 180 | 24 | 170 | 380 | No | 1.0 | 7.5 |
| ASI | 045 | 4.3 | 29 | 50 | 79 | 6.0 | 93 | 180 | No | 0.6 | 13 |
| CAM | 010 | 3.7 | 28 | 110 | 140 | 7.0 | 620 | 800 | No | 0.3 | 19 |
| CAM | 011 | 3.3 | 38 | 46 | 85 | 31 | 100 | 250 | No | 0.8 | 2.7 |
| CAM | 012 | 3.0 | 31 | 56 | 87 | 18 | 63 | 190 | No | 0.5 | 4.9 |
| CAM | 013 | 4.0 | 46 | 58 | 100 | 26 | 99 | 250 | No | 0.8 | 3.9 |
| CAM | 014 | 3.9 | 48 | 62 | 110 | 8.0 | 260 | 380 | No | 0.8 | 14 |
| EUR | 015 | 3.7 | 54 | 110 | 170 | 160 | 1,500 | 2,300 | Yes | 0.5 | 1.1 |
| EUR | 016 | 3.9 | 39 | 40 | 79 | 23 | 640 | 810 | Yes | 1.0 | 3.4 |
| EUR | 017 | 3.0 | 57 | 18 | 75 | 64 | 95 | 260 | Yes | 3.2 | 1.2 |
| EUR | 018 | 4.0 | 36 | 45 | 81 | 81 | 64 | 240 | No | 0.8 | 1.0 |
| EUR | 019 | 3.4 | 33 | 84 | 120 | 65 | 160 | 400 | Yes | 0.4 | 1.8 |
| EUR | 020 | 4.1 | 13 | 76 | 89 | 58 | 1,200 | 1,600 | Yes | 0.2 | 1.5 |
| EUR | 021 | 3.6 | 18 | 23 | 42 | 60 | 88 | 220 | No | 0.8 | 0.7 |
| EUR | 022 | 4.1 | 38 | 25 | 62 | 61 | 120 | 290 | No | 1.5 | 1.0 |
| EUR | 023 | 4.2 | 32 | 31 | 64 | 74 | 130 | 300 | No | 1.0 | 0.9 |
| EUR | 046 | 3.4 | 31 | 21 | 52 | 31 | 39 | 140 | No | 1.5 | 1.7 |
| EUR | 047 | 4.0 | 44 | 49 | 94 | 59 | 45 | 210 | No | 0.9 | 1.6 |
| EUR | 048 | 3.6 | 100 | 65 | 170 | 170 | 190 | 550 | No | 1.6 | 1.0 |
| EUR | 049A[c] | 3.7 | 11 | 20 | 31 | 65 | 59 | 180 | No | 0.6 | 0.5 |
| EUR | 049B[c] | 5.1 | 9.8 | 18 | 28 | 62 | 55 | 160 | No | 0.5 | 0.4 |
| EUR | 050 | 4.0 | 13 | 29 | 43 | 130 | 250 | 440 | No | 0.4 | 0.3 |
| OCE | 029A[c] | 3.8 | 36 | 34 | 70 | 25 | 270 | 420 | Yes | 1.0 | 2.8 |
| OCE | 029B[c] | 5.0 | 75 | 95 | 170 | 21 | 180 | 390 | Yes | 0.8 | 8.3 |
| OCE | 030 | 3.6 | 69 | 87 | 160 | 6.0 | 130 | 300 | No | 0.8 | 27 |
| OCE | 031 | 4.9 | 190 | 85 | 270 | 10 | 85 | 380 | No | 2.2 | 28 |
| OCE | 032 | 4.1 | 36 | 36 | 73 | 14 | 68 | 190 | No | 1.0 | 5.3 |
| OCE | 033 | 3.0 | 160 | 200 | 370 | 4.0 | 1,400 | 1,800 | No | 0.8 | 90 |
| OCE | 034 | 4.2 | 110 | 38 | 140 | 7.0 | 110 | 270 | No | 2.7 | 20 |
| OCE | 051 | 5.4 | 180 | 130 | 310 | 9.0 | 120 | 440 | No | 1.3 | 34 |
| OCE | 052 | 3.9 | 86 | 130 | 220 | 38 | 31 | 290 | No | 0.6 | 5.7 |
| SAM | 024A[c] | 4.3 | 17 | 5.5 | 23 | 29 | 1,900 | 1,900 | Yes | 3.1 | 0.8 |
| SAM | 024B[c] | 5.5 | 20 | 22 | 42 | 7.8 | 500 | 560 | Yes | 0.9 | 5.3 |
| SAM | 024C[c] | 4.6 | 60 | 40 | 100 | 9.9 | 290 | 410 | Yes | 1.5 | 10 |
| SAM | 025 | 3.5 | 49 | 39 | 89 | 27 | 160 | 290 | No | 1.2 | 3.3 |
| SAM | 026 | 3.6 | 30 | 29 | 59 | 5.0 | 380 | 450 | No | 1.0 | 12 |
| SAM | 027 | 3.0 | 51 | 26 | 77 | 17 | 46 | 170 | No | 2.0 | 4.4 |
| SAM | 028 | 3.2 | 34 | 21 | 55 | 9.0 | 80 | 150 | No | 1.6 | 5.8 |
| SAM | 053 | 5.2 | 110 | 140 | 250 | 20 | 210 | 500 | No | 0.8 | 12 |

Note: Shown are the results for each sum parameter in ng/g lipid as well as the SCCP/MCCP and CP/PCB ratios. Sample IDs were assigned according to order of analysis and do not reflect any ranking or geopolitical attributes. All results were rounded to two significant digits for better readability. AFR, Africa; ASI, Asia; CAM, Central America and Caribbean islands; DDT, dichlorodiphenyltrichloroethane; EUR, Europe; ID, identifier; LCCP, long-chain chlorinated paraffin; MCCP, medium-chain chlorinated paraffin; OCE, Australia and Oceania including the Pacific islands; SAM, South America; SCCP, short-chain chlorinated paraffin; ΣIndChem, sum of industrial chemicals; ΣOCPs, sum of chloropesticides; ΣPOPs, sum of persistent organic pollutants; ΣCPs, sum of chlorinated paraffins; ΣMCCPs, sum of medium-chain chlorinated paraffins; ΣPCBs, sum of polychlorinated biphenyls; ΣSCCPs, sum of short-chain chlorinated paraffins.

[a] $C_{18}$–$C_{20}$ CPs.

[b] Sum of all PCBs calculated as sum of marker PCBs (PCB 28, 52, 101, 138, 153 and 180) multiplied with empirical factor 1.6 according to Schulte and Malisch 1984.

[c] Sampled in the same time period in different areas of the country.

level multiplied with three times the standard deviation (SD) as an indicator for the methods limit of detection for human milk (empirical conversion factor, 57.168 μL/g lipid, based on $n = 25$ human milk samples independent of this study) resulted in 4.1 ng/g lipid ΣSCCPs and 4.5 ng/g lipid ΣMCCPs. Multiplying the average blank levels with 10 times the SD, limits of quantification (LOQs)

for human milk in this study were 7.1 ng/g lipid ΣSCCPs and 12 ng/g lipid ΣMCCPs. All sample results were quantifiable (i.e., >LOQ) although four ΣSCCPs and seven ΣMCCPs results were less than a factor of two above the LOQ. The sampling bottles provided to national coordinators were rinsed and sterilized before shipment. Tests with control samples showed that no CPs migrated from the bottles into milk samples. However, it was not possible to account for possible contamination during sampling and pooling in the individual countries beyond recommending a methodology and providing the sterilized and tested sampling bottles.

### *Estimation of Lactational Intake and Health Risk Assessment*

The daily lactational intake (lact. intake) of SCCPs and MCCPs through breastfeeding was calculated according to the following formula:

$$lact.\,intake = (c_{CP} \times mc_d \times l_m)/\mathrm{BW}_{child} \quad (1)$$

where $c_{CP}$ is the sum concentration of SCCPs, MCCPs, or CPs (= sum of SCCPs and MCCPs) in the pooled human milk samples (in nanograms per gram lipid); $mc_d$ is the daily (breast) milk consumption (in grams per day); $l_m$ the relative lipid content of the sample (in grams lipid per gram); and $\mathrm{BW}_{child}$ the body weight (BW) of the nursing infant (in kilograms per body weight). For easier comparison with reported lower-bound 95th confidence interval benchmark dose levels for a 10% change in the critical effect ($\mathrm{BMDL}_{10}$), average milk consumption was assumed to be 800 mL/d, and high consumption was assumed to be 1,200 mL/d for an infant 3 months of age weighing 6.1 kg (EFSA CONTAM Panel et al. 2020). Because the median lipid content in the pooled samples calculated for each of the six geographical areas spanned a narrow range (i.e., 3.9–4.3%), the median value of all pooled samples in the present study (4.1%) was used for calculations. Assuming a specific weight of 1 mL/g for human milk, the daily sample intake was estimated to be 5.4 g lipid/kg BW per day for average consumption and 8.1 g lipid/kg BW per day for high consumption. For risk assessment, we estimated SCCP, MCCP, and CP intakes for average and high milk consumption in each geographic area based on the lowest concentration measured in a pooled sample from the area, the highest concentration in a pooled sample from the area, and the median concentration across all pooled samples from the area. The minimum, median, and maximum lactational intakes based on average and high milk consumption for each area calculated this way are given in Table S4.

For the health risk assessment, a margin of exposure (MOE) approach was chosen. The MOE was calculated based on the estimated daily lactational intake (in nanograms per kilogram BW per day) and the $\mathrm{BMDL}_{10}$ reported for SCCPs and MCCPs by the European Food Safety Authority (EFSA) in 2020 ($2.3 \times 10^6$ ng/kg BW per day and, $36 \times 10^6$ ng/kg BW/d respectively) according to the following formula:

$$MOE = BMDL_{10} \,/\, lact.\,intake \quad (2)$$

Accounting for various sources of uncertainty, the EFSA concluded that an MOE > 1,000 for the dietary intake of SCCPs or MCCPs might indicate that there is no cause for health concern (EFSA CONTAM Panel et al. 2020), so this value was chosen as the limit for the risk assessment. For the conservative risk assessment, MOEs calculated for high milk consumption for each pooled sample were assessed (Table S5), with the lowest MOE of each area standing in for all pooled samples in that geographical area.

### *Statistical Analyses*

Data sets were tested for normal distribution using the Kolmogorov-Smirnov analysis. Correlations between predictors and CPs were analyzed using the Spearman correlation analysis. Clustering of CP results in correlation to PCBs and ΣPOPs concentrations was investigated using *k*-means cluster analysis ($k = 2$–3). The significant level for all operations was set to $\alpha = 0.05$.

## Results

CPs were detected in all pooled human milk samples with a range of 23–700 ng/g lipid (Figure 1, Table 2). The resulting median value of 110 ng/g lipid CPs was ~5 times higher than the

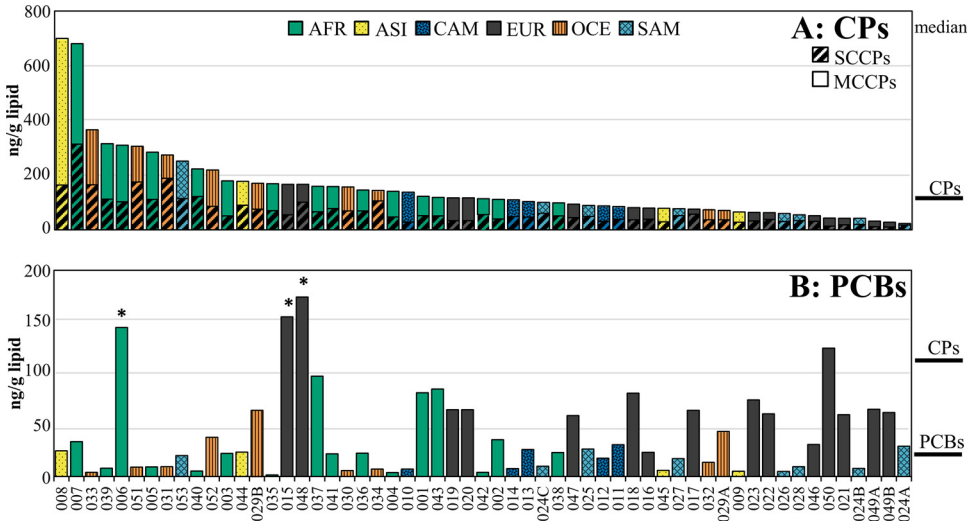


**Figure 1.** Concentrations (ng/g lipid) of chlorinated paraffins (CPs) and polychlorinated biphenyls (PCBs) in 57 human milk samples from 53 countries marked by geographical area (data in Table 1). (A) CPs [sum of short-chain CPs (SCCPs) and medium-chain (MCCPs)] are listed with decreasing CP concentration. The contribution of SCCPs is indicated by the shaded area. On the right-hand side, the median value of CPs is indicated. (B) The total PCB content [calculated according to Schulte and Malisch (1984)] of the same samples is presented. An asterisk above the bars indicates samples with PCB concentrations exceeding the 95th percentile. The right-hand side shows median values of PCBs and CPs. Note: AFR, Africa; ASI, Asia; CAM, Central America and Caribbean islands; EUR, Europe; OCE, Australia and Oceania including the Pacific islands; SAM, South America.

**Table 2.** Concentration ranges of chlorinated paraffins (CPs) in relation to total persistent organic pollutants (POPs) levels (ΣPOPs) in human milk samples from six regions ($n = 57$ collected during 2012–2019).

| Area | AFR | ASI | EUR | CAM | OCE | SAM | All areas |
|---|---|---|---|---|---|---|---|
| Samples ($n$) | 16 | 4 | 15 | 5 | 9 | 8 | 57 |
| SCCPs (ng/g lipid) | 40–310 (68) | 27–160 (59) | 9.8–100 (33) | 28–48 (38) | 36–190 (86) | 17–110 (41) | 9.8–310 (50) |
| MCCPs (ng/g lipid) | 47–370 (94) | 38–540 (69) | 19–110 (31) | 46–110 (58) | 34–200 (87) | 5.6–140 (28) | 5.5–540 (62) |
| SCCPs/MCCPs ratio | 0.4–1.2 (0.7) | 0.3–1 (0.7) | 0.2–3.2 (0.9) | 0.3–0.8 (0.8) | 0.6–2.7 (1) | 0.8–2 (1.3) | 0.2–3.2 (0.8) |
| CPs (ng/g lipid) | 98–680 (160) | 65–700 (130) | 28–170 (75) | 85–140 (100) | 73–370 (170) | 23–250 (68) | 23–700 (110) |
| PCBs (ng/g lipid)[a] | 1.4–140 (23) | 5.2–25 (15) | 23–170 (64) | 7.1–31 (18) | 4.1–38 (9.6) | 4.8–29 (14) | 1–170 (23) |
| CPs/PCBs ratio | 1.4–117 (7.6) | 7.5–28 (13) | 0.3–3.4 (1.1) | 2.7–19 (4.9) | 2.1–90 (23.5) | 3.3–12 (5.1) | 0.3–117 (5.3) |
| DDT (ng/g lipid) | 96–630 (240) | 45–470 (130) | 64–1,500 (130) | 63–620 (100) | 68–1,400 (130) | 46–1,900 (250) | 31–7,100 (160) |
| ΣPOPs[b] (ng/g lipid) | 230–1,000 (670) | 180–850 (460) | 220–2,300 (300) | 180–780 (240) | 170–420 (370) | 290–1,900 (500) | 140–7,300 (390) |
| CP% of ΣPOPs | 14–67% (38%) | 12–83% (45%) | 6–33% (21%) | 18–48% (36%) | 17–73% (43%) | 1–51% (24%) | 9.8–310 (50) |

Note: Values shown are minimum–maximum (median) unless otherwise indicated. The concentration ranges of DDT and PCBs and the CP/PCB ratio were added to emphasize their role in the total POP levels of human milk in comparison with SCCPs or MCCPs. All concentrations were rounded to two significant digits for better readability. AFR, Africa; ASI, Asia; CAM, Central America and Caribbean islands; DDT, dichlorodiphenyltrichloroethane; EUR, Europe; HBCDD, hexabromocyclododecane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; MCCPs, medium-chain chlorinated paraffins; OCE, Australia and Oceania including the Pacific islands; PCBs, polychlorinated biphenyls; PCDD/F, polychlorinated dibenzo-*p*-dioxins and dibenzofurans; SAM, South America; SCCPs, short-chain chlorinated paraffins; ΣIndChem, sum of industrial chemicals; ΣOCPs, sum of chloropesticides; ΣPOPs, sum of persistent organic pollutants.
[a]Sum of all PCBs calculated as sum of marker PCBs (PCB 28, 52, 101, 138, 153 and 180) multiplied with empirical factor 1.6 according to Schulte and Malisch 1984.
[b]Compounds included in ΣPOPs: SCCPs, MCCPs, PCBs, HCB, α/β/γ-HCH, DDT, aldrin, dieldrin, heptachlor, endosulfan, chlordane, endrin, toxaphenes (Parlar 26,50,62), mirex, pentachlorobenzene, hexabromobiphenyl, chlordecone, pentachlorophenol, α/β/γ-HBCDD, and PCDD/Fs.

median PCB concentration of 23 ng/g lipid. CP concentrations from all six regions showed variable distribution, but some trends were observed. The five highest concentrations were found in samples from Asia, Africa, and Oceania, whereas the lowest concentrations were recorded for European and South American countries (Figure 1A). The 75th percentile of CP concentration (170 ng/g lipid) was 2.3 times higher than the 25th percentile (75 ng/g lipid), but still only one-quarter of the highest concentration found in a pooled sample.

In 43 of 57 pooled samples, MCCP concentrations equaled or exceeded SCCPs with a SCCP/MCCP ratio of 0.2–1.0 (median 0.7; Figure 2A). Interestingly, 3 of 9 samples from Oceania, 4 of 8 samples from South America, and 2 of 15 European samples showed a clear dominance (i.e., SCCP/MCCP ratio of >1.5) of SCCPs (Figure 2A, Table 1). Given that the samples with a clear dominance of SCCPs were collected in four different years spanning 2012–2019, we did not attempt to determine whether the shift in SCCP/MCCP ratios toward MCCPs was correlated with the year of sampling. No plausible clusters and no correlation between CPs and PCBs was found for European samples ($n = 15$, Spearman correlation factor $\rho = 0.265$; Table 3; Figure S1). Notably, European pooled samples had some of the highest PCB concentrations in this study, which set them apart from samples of all other regions by approaching or superseding the CP concentrations in 8 of 15 samples (CP/PCB ratio ≤1.0; Figure 2B, Table 1). Two of 3 samples with PCB concentrations above the 95th percentile derived from all samples (130 ng/g lipid) were collected in Europe (Figure 1B, marked with an asterisk), further illustrating the elevated PCB levels found in Europe and Africa. Although the correlation between CPs and PCBs was not significant for European samples according to Spearman analysis, CPs had significant positive correlations with DDT, ΣOCPs, ΣIndChem, and ΣPOPs ($\alpha = 0.05$; Table 3). The concentration ranges of ΣOCPs and ΣPOPs in the other regions were above the range of CPs, whereas ΣIndChem were, in most cases, below the CP level (Figure 3A). In African samples, CPs had a weak positive correlation with DDT ($n = 16$, $\rho = 0.312$; Table 3), whereas CPs in Asian and Central American samples were strongly correlated with all analyte groups investigated, although correlations were not significant because of the small number of pooled samples ($n = 4$ and 5, respectively) from these regions. In Asian, European, and South American samples, CPs were positively correlated with the ΣPCBs ($n = 4$–15, $\rho = 0.143$–1.0; Table 3), whereas in the other regions, especially Central America and the Caribbean, CPs were negatively correlated with the ΣPCBs (CAM, $n = 5$, $\rho = -0.900$). In samples from Asia and South America, CPs were negatively correlated with the ΣDDT and the ΣOCPs ($n = 4$–8, $\rho = -0.800$ to –0.476), whereas in European and Central American samples, CPs were positively correlated with the ΣDDT and the ΣOCPs ($n = 5$–15, $\rho = 0.503$–0.700), which might suggest a different usage pattern of CPs and OCPs in these regions.

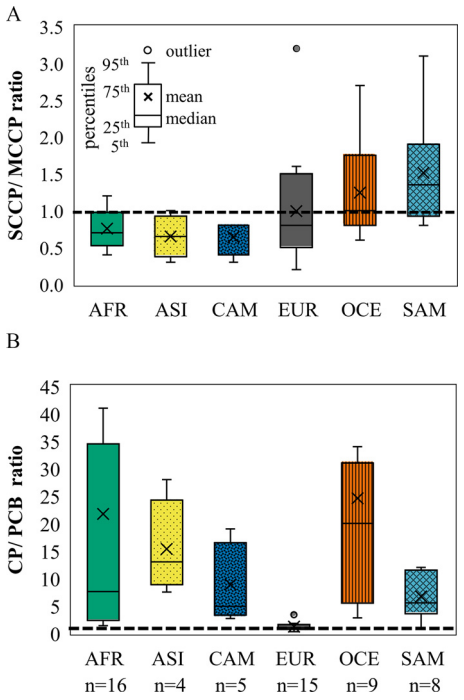


**Figure 2.** Chlorinated paraffins (CPs) in comparison with other persistent organic pollutants (POPs) in human milk samples from six regions ($n = 57$ collected during 2012–2019). (A) ranges of SCCP/MCCP ratios and (B) ranges of CP/PCB ratios differentiated by geographical area. Sample numbers apply to both graphs in this figure, individual results can be found in Table 1. Note: AFR, Africa; ASI, Asia; CAM, Central America and Caribbean islands; EUR, Europe; MCCP, medium-chain chlorinated paraffin; PCB, polychlorinated biphenyl; OCE, Australia and Oceania including the Pacific islands; SAM, South America; SCCP, short-chain chlorinated paraffin.

**Table 3.** Spearman correlation factors ρ ($\alpha = 0.05$) for the correlation between chlorinated paraffins (CPs) and other analytes and analyte groups found in the pooled human milk samples from the respective area.

| Areas | *n* | CPs/PCBs | CPs/DDT | CPs/ΣOCPs | CPs/ΣIndChem | CPs/ΣPOPs | Critical value ($\alpha = 0.05$) |
|---|---|---|---|---|---|---|---|
| All data | 57 | 0.302 | 0.505 | 0.504 | 0.400 | 0.676 | 0.220 |
| AFR | 16 | −0.066 | 0.312 | 0.318 | −0.041 | 0.583 | 0.429 |
| ASI | 4 | 1.000 | −0.800 | −0.800 | 0.800 | 0.400 | 1.000 |
| CAM | 5 | −0.900 | 0.700 | 0.700 | −0.800 | 0.821 | 0.900 |
| EUR | 15 | 0.265 | 0.504 | 0.503 | 0.487 | 0.642 | 0.446 |
| OCE | 9 | −0.383 | 0.100 | 0.059 | 0.133 | 0.567 | 0.600 |
| SAM | 8 | 0.143 | −0.476 | −0.476 | 0.071 | −0.310 | 0.643 |

Note: AFR, Africa; ASI, Asia; CAM, Central America and Caribbean islands; DDT, sum of dichlorodiphenyltrichloroethane and its metabolites; EUR, Europe; OCE, Australia and Oceania including the Pacific islands; PCBs, sum of all polychlorinated biphenyls derived from the sum of marker PCBs; SAM, South America; ΣOCPs, sum of 13 pesticide groups; ΣIndChem, sum of six groups of industrial chemicals and unintentional by-products according to Stockholm Convention; ΣPOPs, total measure of the pooled human milk samples (sum of CPs, ΣOCPs and ΣIndChem).

Of the 21 analyte groups analyzed in the pooled samples (Tables S7 and S8), the four analyte groups contributing most to ΣPOPs were SCCPs, MCCPs, DDT, and PCBs (Figure 3B, Tables 1 and 2; Tables S7 and S9). Although DDT concentrations varied within and among geographic areas, DDT accounted for the largest proportion of ΣPOPs in every region, whereas the relative contributions of the other analytes varied. Median ΣPOPs levels derived for Asian, South American, and African samples (460, 500, and 670 ng/g lipid, respectively; Table 2) were higher than the median levels in other regions (240–370 ng/g lipid). However, the high degree of variation in concentrations among pooled samples from each area, as well as the differences in the number of pooled samples from each area, make definite comparisons very difficult. In individual pooled samples, SCCPs accounted for 0.8% (sample 020, EUR) to 50% (sample 031, OCE) of ΣPOPs, whereas MCCPs accounted for 0.3% (sample 024A, SAM) to 63% (sample 008, ASI) (Table S6). In contrast, there was less variation in the median contribution of CPs to ΣPOPs across pooled samples within the individual regions (range 21–43%) (Table 2).

We had planned to investigate the characteristics of the mothers who contributed to each pooled sample as potential predictors of CP levels, including the contributing mothers' average age, average weight before pregnancy, average height, the proportion with rural vs. urban residences, the proportion employed as something other than a "housewife" before the pregnancy, the proportion who consumed fish more than once a week, and the proportion who consumed sea fish more often than freshwater fish (see Supplemental Material, "Sample summary report"). Age has been shown to influence POP content of human milk samples from primiparas (Albers et al. 1996). The living environment and occupation of the mothers were considered owing to the high findings of CPs in dust and air that could potentially be ingested (Fridén et al. 2011; Hilger et al. 2013). Fish consumption, and especially the percentage of sea fish consumed, was considered owing to findings of CPs and other POPs in sea fish (Krätschmer et al. 2019) and evidence that high fish consumption leads to elevated POP levels in human milk (Fitzgerald et al. 2001). However, because these data were provided for only 27 of the 57

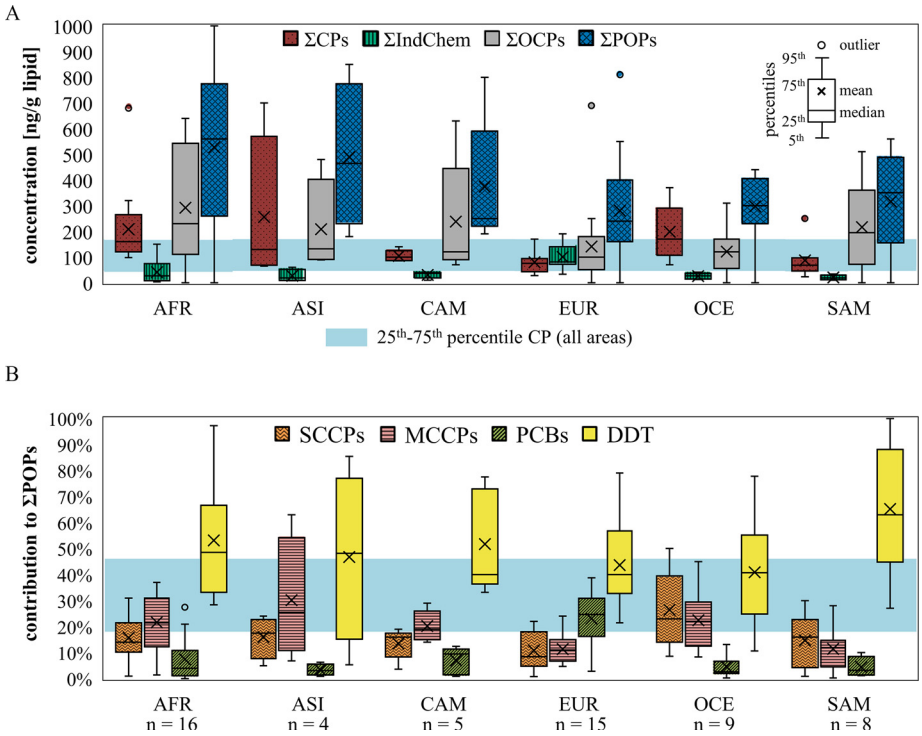


**Figure 3.** Analyte groups and contributions to total persistent organic pollutant (POP) levels of human milk samples from six regions ($n = 57$ collected during 2012–2019). (A) concentration ranges of ΣCPs and the analyte groups (ΣIndChem, ΣOCPs, and ΣPOPs; data in Table S6); (B) percentage ranges of different analytes in relation to ΣPOPs (data in Table S7). The 25th to 75th percentile of all CP data is indicated in both graphs by the shaded area for comparison. Note: AFR, Africa; ASI, Asia; CAM, Central America and Caribbean islands; EUR, Europe; OCE, Australia and Oceania including the Pacific islands; SAM, South America; ΣCPs; ΣIndChem, sum of industrial chemicals; ΣOCPs, sum of chloropesticides; ΣPOPs, sum of persistent organic pollutants.

pooled samples, we did not perform statistical analyses but, rather, report the available sample-specific data only (Tables S1 and S2).

The lactational intake of CPs was estimated for 3-month-old infants (6.1 kg BW) with an (average to high) human milk consumption of 800–1,200 mL per day. The highest CP intakes (assuming high milk consumption) were estimated for infants in Africa and Asia (5,500 and 5,600 ng CPs/kg BW per day, respectively), whereas the lowest lactational CP intake was estimated for infants in Central America (1,100 ng CPs/kg BW per day for high breastmilk consumption) (Table 4; Table S5).

## Discussion

The present study was conducted to assess, on a global scale, the background human exposures to POPs regulated under the Stockholm Convention. A pooled human milk sample approach was chosen because *a*) human milk can be sampled using noninvasive methods; *b*) pooled national samples are less cost intensive and could compensate for variations within the country; and *c*) samples from primiparas represent the mothers' lifelong exposure, thereby giving an indication of general human exposure levels in the respective countries during the previous $\sim 30$ y, excluding influences of active contamination sites based on preselection questionnaires.

We detected CPs in all of the pooled samples ($n = 57$) from 53 individual countries. SCCPs and MCCPs were among the top four analytes contributing to the total concentrations of POPs analyzed for this study, along with DDT (and its metabolites) and PCBs. CP concentrations (i.e., SCCPs and MCCPs combined) were higher than PCB concentrations in almost all individual samples, with the exception of 1 of 8 samples from South America and 8 of 15 samples from Europe. Lactational exposures estimated based on the highest SCCP and MCCP concentrations in each geographical area exceeded the proposed MOE for SCCPs (EFSA CONTAM Panel et al. 2020) in only one case (sample 007, AFR; MOE 920), whereas the lowest MOE for MCCPs in the 57 pooled samples was 8,300 (sample 008, ASI). However, 1 of 4 Asian samples and 3 of 9 Oceanian samples approached the proposed threshold for SCCP exposure (MOE <2,000), indicating that the African pooled sample was not an outlier and that further investigation into human exposure to SCCPs and MCCPs and potential health effects in infants is needed, especially given that individuals might have higher exposures than the pooled samples suggest.

Although the pooled sample study design enabled a cost-effective assessment of the background levels of several POPs in humans from five continents, it also has some limitations. On one hand, pooled samples could compensate for variations, but on the other hand this meant that individual levels (very high or very low) could not be taken into account for risk assessment. The decentralized handling of sampling led to uncertainties pertaining to information that the national coordinators did not report to us —information such as the representativeness and individual characteristics of selected participants or the national protocols for sampling, storing, and shipping individual samples before pooling. Although the national coordinators were asked to collect at least 50 individual samples from donors who were representative of the country as a whole, the donor selection process was not documented, and summary data on the average characteristics of the participants were provided for only 27 of the 57 pooled samples. Consequently, we do not know whether all regions, social groups, or ethnicities were represented in the pooled samples for each country. The number of individual samples in each pool might also influence the generalizability of the pooled samples, particularly when <50 individual samples were included. Time trends could also not be assessed due to the sampling scheme, given that no country presented here participated in different years and the time frame of two surveys in 8 y did not provide enough data points in general for trend analysis.

### *Comparability with Literature*

With just a small number of studies on CPs in human milk available, it is worth noting that results are heavily dependent on sample type given that larger variations in concentration are inherent in individual samples compared with pooled samples. The use of pooled samples compensates for the variation caused by differences in age, diet, living environment, and other factors associated with exposure and thus provides an indication of the more general levels of contamination in each represented area. Mothers living near likely contamination hotspots were excluded, allowing for the investigation of background contamination in each area. Efforts to exclude participants with unusually high exposures have not been taken or have not been reported in many published studies of CPs in human milk (Table 4); one study even specifically surveyed mothers from Hebei Province in China, postulating their likely higher CP exposure due to heavy CP production in the area (Yang et al. 2018). Another difference between studies is the parity of the mothers: Although only primiparas were chosen for the present study, some previous studies did not report parity or included a mix of primiparas and other mothers (Table 4). Therefore, results should be compared with these differences in mind.

As the major producer of CPs, it is unfortunate that a representative nationwide pool sample from China was not available for the present study. Xia et al. (2017a) reported SCCP and MCCP concentrations in pooled human milk samples from provinces and cities in China that, when summed in the samples with the lowest and highest SCCP and MCCP values, indicate total CP concentrations of 82–2,500 ng/g lipid (median = 400 ng/g lipid). In contrast, the range of total CP concentrations in pooled samples from Asian countries in the present study was 65–700 ng/g lipid (median = 130 ng/g lipid) (Table 4). Yang et al. (2018) reported that SCCP concentrations in individual milk samples collected during 2014–2015 from mothers living near a city where CPs are manufactured (Shijizhuang, China), ranged from 0.2 to 16 ng/g lipid. Cao et al. (2017) reported median and maximum SCCP concentrations of 28 and 66 ng/g lipid, respectively, in 17 pooled samples collected from mothers in Beijing, China (2007–2009). In contrast, SCCP concentrations were below the method detection limit (MDL) (i.e., 0.5 ng/g lipid) in 14 of 16 pooled samples from two cities in Korea and <MDL for 38 of 44 pooled samples from two cities in Japan, whereas the maximum concentrations for the Korean and Japanese samples were 3.4 and 18 ng/g lipid, respectively. A study with samples from cities in China, Sweden, and Norway reported SCCPs, MCCPs, and LCCPs (Zhou et al. 2020). The sum of SCCPs (<12–120 ng/g lipid) and sum of MCCPs (<16–310 ng/g lipid) in individual Swedish and Norwegian samples were generally consistent with the European samples in the present study (SCCPs, 9.8–100 ng/g lipid; MCCPs, 19–110 ng/g lipid). Ranges of concentrations in 36 individual Chinese samples collected during 2015–2016 (SCCPs, <12–680 ng/g lipid; MCCPs, <16–1,300 ng/g lipid) were larger, but median concentrations (35 and 79 ng/g lipid, respectively) were generally consistent with our estimates for other Asian countries.

The observation of higher MCCP proportions, particularly in samples above the 90th percentile of ΣCP concentration in the present study (54–77% MCCPs in samples >310 ng/g lipid ΣCP; Table 1), however, was in agreement with an assumed shift away from SCCP production and consumption since the 2000s. This shift should manifest in a lower accumulated SCCP than MCCP exposure in the participants, especially in countries with an

**Table 4.** Comparison of concentration [ng/g lipid, minimum–maximum (median)] and estimated lactational intake [ng/kg BW per day, median–maximum] of SCCPs and MCCPs in the present study with literature data.

| | Sample | | | | | | | Concentration [ng/g lipid] | | | Lactational intake [ng/kg BW per day] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | Year | Type | $n_P$ | $n_I$ | Parity | Hotspots excl. | Urban/rural | SCCPs | MCCPs | CPs[a] | SCCPs | MCCPs | CPs[a] | Reference |
| UK | 2006 | I | 0 | 25 | n.n. | n.n. | U/R | 49–820 (170) | 6.2–320 (21) | 67–840 (210) | n.n. | n.n. | n.n. | Thomas et al. 2006 |
| Sweden | 1996–2010 | I | 0 | 12 | 1 | n.n. | U | 45–160 (110) | <1.1–30 (15) | 47–190 (120) | 460–680 | 61–130 | 520–810 | Darnerud et al. 2012 |
| Norway | 2014 | I | 0 | 8 | n.n. | n.n. | U | <12–120 (23) | <16–310 (51) | 16–310 (60) | 60–140 | 250–520 | 310–660 | Zhou et al. 2020 |
| Sweden | 2011–2016 | I | 0 | 19 | 1 | n.n. | U | <12–28 (16) | <16–78 (30) | 14–100 (42) | 65–110 | 170–290 | 240–400 | Zhou et al. 2020 |
| Germany | 2011 | I | 0 | 60 | n.n. | n.n. | U/R | <37–60 (16) | 9.6–900 (120) | 18–910 (140) | n.n. | n.n. | n.n. | Hilger et al. 2011 |
| EUR | 2014–2019 | N | 16 | >495 | 1 | Yes | U/R | 9.8–100 (33) | 19–110 (36) | 28–170 (75) | 280–810 | 290–900 | 620–1,300 | Present study |
| China | 2007–2009 | RC | 17 | 85 | 1 | n.n. | U | <20–66 (28) | n.n. | n.n. | 330–470 | n.n. | n.n. | Cao et al. 2017 |
| Korea | 2007–2010 | RC | 16 | 80 | 1–2 | n.n. | U | <0.5–3.4 (<0.5) | n.n. | n.n. | 240–250 | n.n. | n.n. | Cao et al. 2017 |
| Japan | 2007–2010 | RC | 44 | 220 | 1–2 | n.n. | U | <0.5–18 (<0.5) | n.n. | n.n. | 240–290 | n.n. | n.n. | Cao et al. 2017 |
| China | 2010 | I | 0 | 13 | 1 | n.n. | U | <12–120 (44) | 38–190 (120) | 38–310 (160) | 170–2,600[b,c] | 120–370[b,c] | 290–3,000 | Zhou et al. 2020 |
| China | 2007–2011 | RP | 24 | 1,412 | 1 | Yes | R | 66–2,300 (300) | 9.1–110 (38) | 82–2,500 (330) | 1,300–8,700[d] | 150–550[d] | 1,500–9,300 | Xia et al. 2017a |
| China | 2007–2011 | RP | 28 | 1,370 | 1 | Yes | U | 131–16,100 (680) | 22–1,500 (64) | 150–17,600 (750) | n.n. | n.n. | n.n. | Xia et al. 2017b |
| China | 2014–2015 | I | 0 | 86 | n.n. | No | U/R | 0.21–16 (2.5) | n.n. | n.n. | 7,100 | n.n. | n.n. | Yang et al. 2018 |
| China | 2015–2016 | I | 0 | 23 | 1–2 | n.n. | U | <12–680 (35) | <16–1,300 (66) | 16–1,900 (92) | 170–2,600[b] | 120–370[b] | 290–3,000 | Zhou et al. 2020 |
| ASI | 2018–2019 | N | 4 | >100 | 1 | Yes | U/R | 27–160 (60) | 38–540 (69) | 65–700 (130) | 480–1,300 | 560–4,300 | 1,000–5,600 | Present study |
| OCE | 2013–2019 | N | 9 | >75 | 1 | Yes | U/R | 36–190 (86) | 34–200 (87) | 73–370 (170) | 770–1,500 | 690–1,600 | 1,500–3,000 | Present study |
| AFR | 2015–2019 | N | 16 | >312 | 1 | Yes | U/R | 40–310 (68) | 47–370 (94) | 98–680 (160) | 550–2,500 | 750–3,000 | 1,300–5,500 | Present study |
| CAM | 2015–2018 | N | 5 | >101 | 1 | Yes | U/R | 28–48 (38) | 46–110 (58) | 85–140 (100) | 310–390 | 460–880 | 830–1,100 | Present study |
| SAM | 2012–2019 | N | 8 | >149 | 1 | Yes | U/R | 17–110 (41) | 5.6–140 (28) | 55–250 (77) | 330–920 | 220–1,100 | 1,400–2,000 | Present study |

Note: Lactational intake results of the present study were calculated for the median to highest concentration in the pooled samples of each region and high milk consumption (1,200 mL/d, 4.1% lipid) of the infant. The full range of lactational intake is shown in Tables S4 and S5. The number of individual participants for each area in the present study is reported as minimum number based on the 27-sample summary reports received. Results below the MDL are reported as <(value of MDL) in the concentration ranges. AFR, Africa; ASI, Asia; CAM, Central America and Caribbean islands; EUR, Europe; hotspots excl., hotspots excluded; I, individual samples; MCCPs, medium-chain chlorinated paraffins; MDL, method limit of detection; N, national pooled samples; $n_I$, number of individual participants; n.n., unknown; $n_P$, number of pooled samples; OCE, Australia and Oceania including the Pacific islands; R, rural residence of mothers; RC, regionally pooled samples (pooled by city); RP, regionally pooled samples (by province); SAM, South America; SCCPs, short-chain chlorinated paraffins; U, urban residence of mothers.

[a]Sum of SCCPs and MCCPs.

[b]50th–90th percentile.

[c]No differentiation between sampling years for this calculation.

[d]50th–95th percentile.

elevated CP exposure as represented by the 90th percentile of ΣCP concentrations. Limited data on SCCPs and MCCPs in human milk available from 2006–2012 (Thomas et al. 2006; Darnerud et al. 2012) indicated a clear dominance of SCCPs (e.g., United Kingdom 2006 median SCCP/MCCP ratio of 7.2). Two studies of samples collected from Chinese donors in 2007 and 2011 indicated a dominance of SCCPs over MCCPs by a factor of 10 (Xia et al. 2017a, 2017b). In contrast, Zhou et al. (2020) indicated in their study an almost equal distribution with a slight dominance of MCCPs for their Chinese samples, excluding Jiaxing province (48–57% MCCP contribution to total CPs collected in 2010 or 2015–2016), whereas most of their European samples (collected in 2011, 2014, and 2016) were clearly dominated by MCCPs (65–71% contribution to total CPs; Zhou et al. 2020). This increasing dominance of MCCPs over SCCPs is especially notable taking into account that primiparous lactation represents the mother's exposure from birth (Albers et al. 1996) because higher MCCP concentrations suggest that accumulated SCCP exposures in the mothers were lower than accumulated exposures to MCCPs, even though the ban on SCCPs only came into effect in 2017. However, differences between studies might reflect regional variation or sample pools that are not representative of the country as a whole, particularly in large or diverse countries, such as China. As also previously mentioned, information about the parity of study participants is not always available, and concentrations reported by previous studies may not represent lifelong POPs exposures.

### *Contribution to POPs*

The high contribution of CPs to the total sample contamination was mostly due to the predominance of DDT (Table 2, Figure 3B; Table S7). In European samples, CPs accounted for a smaller proportion of the total contamination owing to the higher levels of PCBs. CPs were always among the three most abundant POPs. Even when considered separately, SCCPs and MCCPs were among the five most abundant analytes found in all samples (Table 2, Figure 3B; Tables S7 and S8).

Apart from MCCPs, all other compounds and compound classes contributing to ΣPOPs have been banned (with few minor exceptions). Given the continual high production volume of MCCPs and the observed dominance of higher ΣMCCP proportions (35 of 57 samples had a SCCP/MCCP ratio of <1.0), it is very likely that CP levels in human milk will not decrease due to the partial ban on SCCPs but, rather, level out or further increase in the coming years. In the human milk samples from Asia, Africa, Central America, and Oceania, median CP contribution to total POPs ranged from 36% to 45% compared with the median percentages of 21% and 24% for CPs in European and South American samples, respectively (Table 2).

Notably, 33% of the individual sample pools provided the first indications of the presence of LCCPs, in addition to SCCPs and MCCPs, with 16 of the 19 samples presenting equal amounts or a dominance of MCCPs over SCCPs (Table 1). Industry in countries party to the Stockholm Convention (notably not India, China, or the United States) is expected to have shifted from SCCPs to CP products with longer carbon chains; this should soon be reflected in MCCP dominance and a dwindling level of SCCPs in human milk samples, allowing for some delay for accumulation in consumers. However, commercial CP technical products from the Asia–Pacific industry sector are known to contain a mix of different CP groups (Li et al. 2018), so findings of LCCPs alongside MCCPs are expected to increase in the coming years, potentially resulting in yet another subclass of CPs in need of risk assessment and regulation.

### *Exposure Estimation and Risk to Infants*

The central questions about the main exposure pathways and biodegradation or metabolism of CPs in the human body are hitherto unanswered. Both diet and consumer behavior are important factors for human exposure to CPs: When released into the environment, POPs accumulate through the food chain in lipid-rich tissues of animals, leading to human exposure via dietary intake (Albers et al. 1996; Fitzgerald et al. 2001; Abballe et al. 2008; Houde et al. 2008; Mamontova et al. 2017; Polanco Rodríguez et al. 2017). Although the occurrence of CPs in food has been established (Iino et al. 2005; COT 2009; Krätschmer et al. 2019), the dietary intake of CPs estimated based on unprepared food alone cannot account for the CP levels in human milk. Instead, additional sources need to be taken into account. For instance, high CP levels were reported in indoor dust (Fridén et al. 2011; Hilger et al. 2013) and kitchen appliances (Yuan et al. 2017; Gallistl et al. 2018). It is therefore possible that a noticeable contribution to total CP exposure may arise from increased dietary intake due to carryover contamination during food preparation by contact with consumer products or direct exposure through ingestion of dust, dermal absorption, or inhalation of CPs released from consumer products (Fridén et al. 2011; Gallistl et al. 2017; Wang et al. 2019).

A distinct lack of toxicological and metabolomics studies on CPs makes the evaluation of our results from a toxicological point of view very difficult. Many of the available studies on CPs in humans were conducted decades ago and can only serve as indicators toward severe adverse effects on human health; especially concerning the perinatal exposure of infants through human milk, further studies are necessary (El-Sayed and Legler 2010). According to newer transfer studies, CPs in human milk are likely to have been in maternal blood as well (Chen et al. 2020), which was shown through paired maternal and umbilical cord serum samples to signify a transfer to the offspring through the placenta (Qiao et al. 2018). In 2020, the EFSA adopted the benchmark dose levels ($BMDL_{10}$s) of 2.3 mg/kg BW per day for SCCPs based on evidence of increased nephritis in male rats at this exposure level and 36 mg/kg BW per day for MCCPs based on evidence of increased relative kidney weights in male and female rats (EFSA CONTAM Panel et al. 2020). No $BMDL_{10}$ could be established for LCCPs, although the kidneys were identified as likely target organs (EFSA CONTAM Panel et al. 2020). The lactational exposures calculated for pooled samples in the present study are below the $BMDL_{10}$ (MOE = 1,000, Table 4). However, estimates for some African and Asian countries approach the MOE (Table S5). The estimated lactational intakes reported in the literature mirror the variations in SCCP and MCCP concentrations in the human milk samples. The estimated lactational intake of SCCPs in Europe [60–680 ng/kg BW per day (Darnerud et al. 2012; Zhou et al. 2020)] is in good agreement with our European results, whereas estimations for MCCPs are at least in the same order of magnitude. Notably, the maximum estimated lactational intakes reported for SCCPs in four of five Chinese studies [2,600–8,700 ng/kg BW per day (Xia et al. 2017a, 2017b; Yang et al. 2018; Zhou et al. 2020)] surpassed the MOE, indicating a possible health concern for breastfeeding infants, whereas the Asian pooled samples from the present study, not including a Chinese pool, did not even approach this level (Table 4). Contrastingly, the MCCP intake for the same samples is one order of magnitude lower than our Asian results; indicating a difference in SCCP/MCCP ratio between some Chinese regions and other Asian countries.

A modeling study estimated the half-life of SCCPs, MCCPs, and LCCPs in the human body to be 5.2, 1.2, and 0.6 y, respectively (Dong et al. 2020). This is on the lower end of the range

determined for some PCBs (3.7–19 y) and *p*,*p*′-dichlorodiphenyldichloroethylene (7.6–17 y) in the case of SCCPs, but much shorter for the other CP groups (Bu et al. 2015). Further consequences for chronic toxicity models and subsequent risk assessments are still to be determined, but our data suggest that the industry's supposed shift in CP production toward longer chain lengths has already reached consumers. This emphasizes the need for adequate risk assessment and regulation of these compound classes now more than ever.

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